Baseline left ventricular function and surgical annular stiffening to predict outcome and reverse left ventricular remodeling after undersized annuloplasty for intermediate-degree ischemic mitral regurgitation

Marco Pocar, MD, PhD, Davide Passolunghi, MD, Andrea Moneta, MD, Alessandra Di Mauro, MD, Alda Bregasi, MD, Roberto Mattioli, MD, and Francesco Donatelli, MD, FETCS

Objective: We sought to identify determinants of clinical and functional outcome after myocardial revascularization and associated undersized annuloplasty in patients with intermediate-degree ischemic mitral regurgitation.

Methods: Fifty-seven patients with 2+ or 3+ ischemic mitral regurgitation underwent coronary bypass surgery and implantation of undersized semirigid or flexible complete ring or autologous pericardial band and were followed up to 8.6 years.

Results: Operative mortality was 5%. Baseline left ventricular end-systolic volume index, the strongest multivariable predictor of early postoperative outcome, was correlated with end-systolic volume index ($P < .001$, $R^2 = 0.67$) and ejection fraction ($P < .001$, $R^2 = 0.40$) after repair. More compromised ejection fraction and end-systolic volume index predicted comparatively greater early functional improvement but higher residual postoperative end-systolic volume index ($P < .01$). Cox multivariable analysis identified wall motion as the best baseline predictor of late death and heart failure and regional inferoposterior wall motion as the strongest predictor of recurrent mitral regurgitation ($P \leq .01$). More rigid annuloplasty carried a higher probability of functional recovery in terms of ejection fraction, wall motion, and the occurrence and earlier timing of left ventricular reverse remodeling, expressed by different degrees of end-systolic volume index reduction ($P < .001$, hazard ratio >6).

Conclusions: Combination of undersized mitral annuloplasty and coronary revascularization presents low operative mortality and determines left ventricular unloading in patients with intermediate-degree ischemic mitral regurgitation. Global and regional wall motion are powerful predictors of late outcome. Stiffer mitral annular repair promotes functional recovery and predicts higher probability and earlier timing of reverse remodeling. (J Thorac Cardiovasc Surg 2010;139:1529-38)

Ischemic mitral regurgitation (MR) is a common determinant of adverse prognosis in ischemic heart disease. Surgical correction of severe MR at the time of coronary artery bypass grafting (CABG) is recommended, but optimal management of intermediate-degree MR is more controversial.[1-5] Furthermore, combined mitral surgery may be judged unwise for patients with comorbidities.[6,7] Although previous experience also supports repair for patients with mild-to-moderate ischemic MR,[8] data from randomized trials are scarce,[9] and benefits related to long-term outcome remain to be ascertained.[9,10] Controversy also exists regarding the variability of prosthetic devices and surgical techniques.[11]

From the Department of Cardiovascular Sciences, University of Milan, Milan, Italy.
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Address for reprints: Marco Pocar, MD, PhD, Dipartimento di Scienze Cardiovascolari, Università degli Studi di Milano, IRCCS MultiMedica, Via Milanese 300, 20099 Sesto San Giovanni, Milano, Italy (E-mail: marco.pocar@unimi.it).
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MATERIALS AND METHODS

Patients

Cases of all patients with 2+ or 3+ ischemic MR who underwent undersized mitral annuloplasty and associated CABG between 2000 and 2007 at our institution were retrospectively analyzed. The study population comprised a consecutive series of 57 patients. All patients had previous myocardial infarction at least 16 days before surgery.[10] Exclusion criteria were as follows: emergency operation, residual 2+MR before discharge, and associated cardiac procedures other than tricuspid valve repair (n = 4). Preoperative characteristics are summarized in Table 1. Unless otherwise specified, definitions refer to EuroSCORE criteria.

Surgery and Perioperative Course

Operations were performed through median sternotomy with mildly hypothermic cardiopulmonary bypass (32°C core temperature) and intermittent antegrade-retrograde cold blood cardioplegia with controlled reperfusion. The mitral valve was accessed through a conventional left atriotomy (n = 46) or transseptally (n = 11). Analogously with other reports,[12] the annulus was reduced by 2 sizes with the implantation of a prosthetic complete semirigid ring (n = 10, Carpentier-Edwards Physio; Edwards Lifesciences, Irvine, Calif) or complete flexible ring (n = 24, St Jude Tailor; St Jude Medical, Inc, St Paul, Minn) or with a glutaraldehyde-fixed autologous posterior pericardial band calibrated on a Carpentier-Edwards ring sizer (n = 23). There was a progressive shift toward a more rigid repair, which reflected a general attitude of our group rather

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
ICU = intensive care unit
LV = left ventricular
LVEF = left ventricular ejection fraction
LVESVI = left ventricular end-systolic volume index
MR = mitral regurgitation
WMSI = wall motion score index
WMSInf = regional inferior wall motion score index

than specific preferences of different operating surgeons. All patients received an internal thoracic artery graft to the left anterior descending branch.

Operative deaths include hospital and 30-day mortalities. High-dose inotropic support refers to epinephrine infusion rates at least 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A complicated postoperative course was defined as the placement of intra-aortic balloon pump counterpulsation, high-dose inotropic support, or intensive care unit (ICU) stay at least 5 days.

Echocardiographic Evaluation

Left ventricular (LV) volumes and LV ejection fraction (LVEF) were assessed by the biplane Simpson method. Wall motion score index (WMSI) was calculated according to a 16-segment model and a 3-grade scale, referring to normokinesia, hypokinesia, and akinesia. Four of 912 total segments, coded as grade 4 and indicating localized dyskinesia in 3 patients, were entered as grade 3. MR was graded as 0 (absent), 1+ (mild), 2+ (moderate), 3+ (moderately severe), or 4+ (severe) on the basis of color Doppler extent and spatial distribution of the regurgitant jet relative to left atrial area.

The following variables were analyzed as potential outcome predictors both preoperatively and early postoperatively, after ICU discharge: LV end-diastolic and end-systolic diameters and volumes (crude and indexed to body surface area), left atrial anteroposterior and longitudinal diameters, LVEF, WMSI, and MR degree. The following preoperative variables were also analyzed: LV sphericity (expressed as end-diastolic major axis/minor axis ratio), regional inferior WMSI (WMSInf, calculated as the mean wall motion score of the 6 basal and midventricular posteroseptal, inferior, and posterior segments), percentage of akinetic segments, coaptation depth of the tethered leaflets,[13] central versus eccentric regurgitant jet, degree of tricuspid regurgitation, and systolic pulmonary arterial pressure. Postoperative LVEF, WMSI, LV end-systolic volume index (LVESVI), and their respective variations, expressed as postoperative to preoperative ratios, were analyzed to depict functionally the early response to surgery, residual LV dysfunction, and the occurrence of early reverse remodeling, defined as at least 10% reduction in LVESVI.

Follow-up

Late data were obtained from clinical follow-up, telephone interviews, or both. All survivors underwent echocardiography at least 6 months after the operation. All-cause and cardiac-related deaths (including operative mortality), recurrent heart failure (New York Heart Association class ≥3), and recurrent MR (≥3+ or ≥2+) were analyzed as late adverse events. Functional end points were as follows: sustained improved LVEF, WMSI, or LVESVI (late/early postoperative ratio >1 for LVEF or <1 for WMSI and LVESVI); a 5% or 10% LVEF increment from baseline; and late reverse remodeling, defined as at least 10% LVESVI postoperative reduction or 15% or 20% LVESVI reduction from baseline.

TABLE 1. Preoperative characteristics (n = 57)

Age (y)	
Mean ± SD	69.1 ± 7.6
Range	53–82
Sex (male/female ratio)	39:18
Chronic pulmonary disease (no.)	24 (42.1%)
Extracardiac arteriopathy (no.)	32 (56.1%)
Neurologic dysfunction (no.)	8 (14.0%)
Creatinine >180 μmol/L (no.)	14 (24.5%)
Previous cardiac surgery (no.)	4 (7.0%)
Urgent operation (no.)	10 (17.5%)
Critical preoperative state (no.)	12 (21.1%)
Intravenous nitrates (no.)	17 (29.9%)
Left bundle branch block (no.)	14 (24.5%)
New York Heart Association functional class	
Mean ± SD	2.9 ± 0.6
II (no.)	10 (17.5%)
III (no.)	39 (68.4%)
IV (no.)	8 (14.0%)
Infarction–surgery interval (mo, mean ± SD)	64.0 ± 95.4
Inferoposterior/anterior infarction ratio	
No.	44:13
%	77.2%:22.8%
Pulmonary arterial pressure (mm Hg, mean ± SD)	44 ± 10
Additive EuroSCORE (mean ± SD)	9 ± 4

Early data were 100% complete. Two patients from remote areas could not be traced, however, accounting for a 96.3% completeness of late follow-up.

Statistical Analysis

Continuous variables are expressed as mean ± SD unless otherwise specified. The 2-tailed *t* test was used to compare means. The χ^2 test or Fisher's exact test when appropriate and binary logistic regression were used for univariable and multivariable analyses of early outcome. Predictors with a trend toward significance ($P < .10$) were entered into the multivariable analysis. Receiver operating characteristic curves served to identify cutoff values of significant predictors. The Cox proportional hazard model served to identify predictors of late events with time, testing preoperative and early postoperative covariates separately. Two blocks of 11 preoperative variables (age, infarction–surgery interval, LVEF, WMSI, WMSInf, percentage of akinesia, LVESVI, coaptation depth, sphericity, annuloplasty technique, and ring size) and 6 early postoperative variables (complicated course, LVEF, improved LVEF, WMSI, LVESVI, and ≥10% LVESVI early reduction) were entered as covariates. Annuloplasty technique was coded as *0* for pericardial annuloplasty, *1* for flexible ring, and *2* for semirigid ring implantation to create a mitral annular stiffening score. Relationships between 8 baseline continuous variables (infarction–surgery interval, LVEF, WMSI, WMSInf, percentage of akinesia, LVESVI, coaptation depth, and sphericity) and 6 early postoperative continuous variables (LVEF, WMSI, LVESVI, and their respective improvements expressed as postoperative/preoperative ratios) were outlined with linear regression analysis. Probabilities of late events and differences in probability estimates were calculated with the Kaplan–Meier method and the log-rank test. SPSS software for Windows (version 13.0; SPSS, Inc, Chicago, Ill) was used for computations.

RESULTS

Early Outcome

Three operative deaths (5.3%) occurred 5, 11, and 23 days after the operation. The causes of death were as

follows: sudden cardiac death 2 days after ICU discharge, refractory heart failure, and respiratory insufficiency. Although purely indicative (in view of the different techniques and sizers), ring size after repair was 26.8 ± 1.0 (range, 24-30). Myocardial revascularization was complete (2.5 ± 0.9 grafts/patient). Cardiopulmonary bypass and aortic crossclamp times were 158 ± 36 and 106 ± 25 minutes, respectively. ICU stay averaged 6 ± 5 days, whereas intra-aortic balloon pump, high-dose inotropic support, and ICU stay of at least 5 days were required in 5, 31, and 32 cases, respectively, accounting for a fully uncomplicated postoperative course in only 13 of 57 cases (22.8%). Multivariable analysis failed to identify independent predictors of early death. Similarly, no preoperative variable could anticipate a prolonged ICU stay, but a higher LVESVI did predict a complicated postoperative course as a cumulative event ($P = .009$).

MR degree ($P < .001$), WMSI ($P = .01$), and all atrial and ventricular end-diastolic and end-systolic dimensions ($P < .001$) improved significantly early after repair, but LVEF did not ($P = .46$; Table 2), whereas several functional variables independently predicted the perioperative outcome (Table 3). Older infarcts determined a higher probability of improved WMSI or LVESVI but also of a lower LVEF. More specifically, surgery at least 24 months after myocardial infarction anticipated a higher probability of a LVEF of 35% or less after the operation ($P = .001$, area under the curve 0.75; sensitivity 72.4%, specificity 71.4%), but a lower baseline LVEF showed a higher probability of improvement. Notably, all patients with baseline LVEF lower than 30% had improvement, and a LVEF of 36% or less discriminated patients more likely to have improvement ($P < .001$, area under the curve 0.80, sensitivity 77.8%, specificity 56.7%). Baseline LVESVI showed the highest number of significant correlations with early outcome variables. In particular, a higher LVESVI predicted worse postoperative LVEF and LVESVI but also a higher probability of early LVESVI reduction; that is, of early LV reverse remodeling. LVESVI of at least 54 mL/m^2 predicted an early postoperative LVESVI of at least 45 ml/m^2 ($P < .001$, area under the curve 0.89, sensitivity 87.5%, specificity 84.8%).

The strongest baseline predictors of postoperative LVESVI, LVEF, and LVEF variation are illustrated in Figure 1.

TABLE 2. Perioperative variation of functional variables

	Preoperative	Postoperative	*P* value
LV ejection fraction (%, mean ± SD)	36.21 ± 9.48	37.07 ± 8.38	.46
Wall motion score index (mean ± SD)	1.94 ± 0.33	1.83 ± 0.36	.01
Left atrial diameter (mm, mean ± SD)			
Anteroposterior	45.68 ± 5.46	43.09 ± 4.12	<.001
Longitudinal	58.07 ± 6.59	54.00 ± 5.27	<.001
LV diameter (mm, mean ± SD)			
End-diastolic	59.89 ± 5.92	56.51 ± 5.35	<.001
End-systolic	46.11 ± 7.82	42.53 ± 7.89	<.001
LV volume (mL, mean ± SD)			
End-diastolic	144.39 ± 40.45	121.67 ± 36.34	<.001
End-systolic	91.40 ± 33.59	77.00 ± 29.80	<.001
LV diameter index (mm/m^2, mean ± SD)			
End-diastolic	33.95 ± 3.84	32.05 ± 3.66	<.001
End-systolic	26.12 ± 4.57	24.12 ± 4.74	<.001
LV volume index (mL/m^2, mean ± SD)			
End-diastolic	81.37 ± 21.51	68.75 ± 20.53	<.001
End-systolic	51.59 ± 18.74	43.47 ± 16.77	<.001
Mitral regurgitation degree (mean ± SD)	2.47 ± 0.60	0.56 ± 0.50	<.001

LV, Left ventricular.

Late Results

Predictors of late events at Cox regression analysis are specified in Table 4. At a mean follow-up of 43 ± 29 months (median, 40 months; interquartile range, 19–63 months; longest observation, 103 months), 12 late deaths were recorded. Nine (75%) were cardiac related. Remaining causes of death were stroke and end-stage lower extremity vascular disease in 2 patients and 1 patient, respectively. Thus the cause of death was always a major cardiovascular event. Cardiac deaths were related to end-stage heart failure in 5 instances and sudden cardiac death or recurrent myocardial infarction in 2 cases each. The survival curve (Figure 2, *A*) showed an early 6-month higher-risk phase, an intermediate lower-risk interval, and a late, more rapidly declining phase more evident after 4 to 5 years. Probabilities of survival (±SE) were 90.8% ± 3.9%, 89.0% ± 4.2%, 86.5% ± 4.8%, 65.9% ± 9.0%, and 50.5% ± 10.4%, respectively, at 6 months and 1, 3, 5, and 7 years after surgery. Curves for all-cause and cardiac-related mortalities were similar. Baseline and early postoperative WMSI were the sole predictors of late all-cause and cardiac-related mortalities at Cox multivariable analysis, with a 0.1 increment determining a nearly 25% higher probability of late death ($P = .01$; Figure 2, *B*). The predictive strengths of preoperative global and regional WMSI values were confirmed by Kaplan–Meier analysis ($P = .02$ for WMSI ≥2, $P = .003$ for WMSInf ≥2.2). The latter also suggested different probabilities of late survival in relation to preoperative sphericity of 1.3 or less ($P = .01$) and early postoperative LVESVI of at least 45 mL/m^2 ($P = .009$), but these trends were not confirmed by multivariable analysis.

Heart failure, 3+MR, and 2+MR recurred in 9 patients (17.3%), 5 (9.6%), and 19 (36.5%), respectively (Figure 2, *C–E*). Probabilities of freedom from heart failure and recurrent MR at least 2+ among operative survivors (±SE) were 98.1% ± 1.9%, 96.1% ± 2.7%, 91.0% ± 4.3%, 86.2% ± 6.2%, and 71.1% ± 11.0%, and 100%, 100%, 97.2% ± 2.7%, 86.0% ± 7.9%, and 86.0% ± 7.9%, respectively at 6 months and 1, 3, 5, and 7 years after repair. One patient

ACD

TABLE 3. Multivariable predictors of early outcome

				LVEF		WMSI		LVESVI			
	High-dose inotropic support	IABP	Complicated course	≤35%	Improved	≥2	Improved	≥45mL/m²	≥50mL/m²	Improved	Reduced ≥10%
Intravenous nitrates											
P	—	.033	—	—	—	—	—	—	—	—	—
Odds ratio	—	12.00	—	—	—	—	—	—	—	—	—
95% CI	—	1.23–117.25	—	—	—	—	—	—	—	—	—
Left bundle branch block											
P	—	—	—	—	—	.020	.017	—	—	—	—
Odds ratio	—	—	—	—	—	5.68	0.13	—	—	—	—
95% CI	—	—	—	—	—	1.31–24.63	0.02–0.69	—	—	—	—
AMI–surgery interval (mo)											
P	—	—	—	.010	—	—	.046	—	—	.044	—
Odds ratio	—	—	—	1.03	—	—	1.01	—	—	1.04	—
95% CI	—	—	—	1.01–1.05	—	—	1.00–1.03	—	—	1.00–1.07	—
Anterior AMI											
P	—	—	—	—	—	.016	—	—	—	—	—
Odds ratio	—	—	—	—	—	7.86	—	—	—	—	—
95% CI	—	—	—	—	—	1.48–41.79	—	—	—	—	—
LVEF (%)											
P	.04	—	—	—	<.001	—	—	—	—	—	—
Odds ratio	0.94	—	—	—	0.75	—	—	—	—	—	—
95% CI	0.88–1.00	—	—	—	0.64–0.89	—	—	—	—	—	—
WMSI ≥2											
P	—	—	—	—	—	—	—	—	.039	—	—
Odds ratio	—	—	—	—	—	—	—	—	10.64	—	—
95% CI	—	—	—	—	—	—	—	—	1.13–100.39	—	—
WMSI, 6 inferior segments ≥2.2											
P	—	—	—	—	—	.021	—	—	—	—	—
Odds ratio	—	—	—	—	—	5.89	—	—	—	—	—
95% CI	—	—	—	—	—	1.30–26.71	—	—	—	—	—
Akinetic segments ≥25%											
P	—	—	—	—	—	—	.004	—	—	—	—
Odds ratio	—	—	—	—	—	—	8.67	—	—	—	—
95% CI	—	—	—	—	—	—	1.99–37.72	—	—	—	—
LVESVI											
P	—	—	.009	.010	.050	—	—	<.001	.008	—	.009
Odds ratio	—	—	1.06	1.07	0.94	—	—	1.14	1.10	—	1.05
95% CI	—	—	1.01–1.11	1.02–1.12	0.89–1.00	—	—	1.06–1.22	1.02–1.18	—	1.01–1.09

IABP, Intra-aortic balloon pump; *LVEF,* left ventricular ejection fraction; *WMSI,* wall motion score index; *LVESVI,* left ventricular end-systolic volume index; *CI,* confidence interval; *AMI,* acute myocardial infarction.

required reoperation after 48 months and underwent bioprosthetic valve replacement. Preoperative WMSI and early postoperative LVESVI predicted adverse events at multivariable analysis. WMSI was the strongest predictor of recurrent heart failure ($P = .01$). No preoperative variable reached statistical significance with respect to recurrent 3+ MR, but WMSInf predicted late 2+MR ($P = .009$; Figure 2, *F*). Conversely, early postoperative LVESVI predicted late heart failure ($P = .02$) and 3 + MR ($P = .02$) and showed a strong trend toward significance with respect to late 2 + MR ($P = .06$). At Kaplan–Meier analysis, the strongest indicator of adverse events excluding death was a WMSInf of 2.2 or greater, which predicted recurrent heart failure ($P = .008$) and 2 + MR ($P = .001$). Coaptation depth of at least 1 cm was also identified as a predictor of adverse events ($P = .01$ for heart failure, $P = .004$ for 2 + MR) but not at multivariable analysis.

The analysis of stability and improvement of ventricular function (LVEF, WMSI, and LVESVI) during follow-up demonstrated how patients with worse baseline and early postoperative LVEF or with a more dilated LV early after repair showed a higher probability of further late improvement. A poorer WMSI early after surgery, however, predicted a lower probability of late improvement in terms

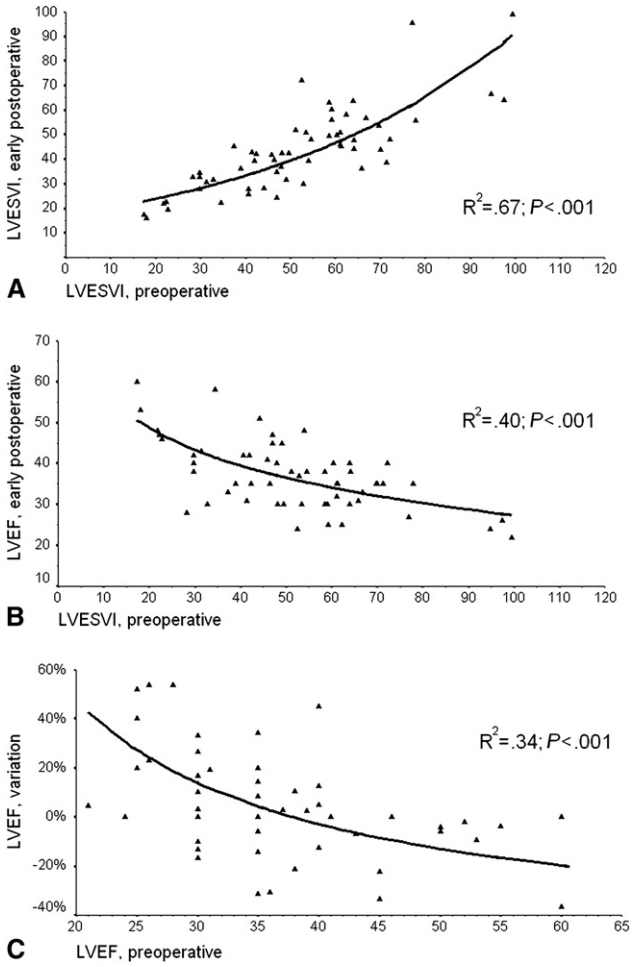

FIGURE 1. Relationships depicting strongest predictors of early postoperative left ventricular end-systolic volume index *(LVESVI)*, left ventricular ejection fraction *(LVEF)*, and left ventricular ejection fraction variation.

of LVEF ($P = .03$) and LVSEVI ($P = .01$). Furthermore, a complicated postoperative course determined a 4- to 5-fold probability of worsened late WMSI ($P < .001$) and LVESVI ($P = .03$). Interestingly, the sole preoperative variable other than baseline LVEF to predict stable or improved late LVEF was sphericity ($P = .03$).

Kaplan–Meier analysis outlined a relatively constant probability of LV reverse remodeling with time, expressed as LVESVI reduction of at least 20% from baseline, which resulted in probability values of (±SE) 1.9% ± 1.9%, 1.9% ± 1.9%, 25.1% ± 6.6%, 43.4% ± 8.5%, and 54.0% ± 10.0%, at 6 months and 1, 3, 5, and 7 years after repair (Figure 3A). The probability of functional benefit was comparatively higher for patients with a preoperative LVESVI of at least 50 mL/m^2 ($P = .001$; Figure 3, *B*). Similarly, multivariable analysis showed the predictability of late reverse remodeling by a higher baseline ($P < .01$) or early postoperative LVESVI ($P = .047$).

Notably, a more rigid mitral annular stabilization strongly predicted the probability of stable or improved late LVEF, WMSI, and LVESVI ($P < .001$) at multivariable analysis. Most importantly, a stiffer annulus predicted late LVEF improvement and the occurrence and earlier timing of LV reverse remodeling ($P \leq .001$). Kaplan–Meier analysis generated similar observations ($P < .001$; Figure 3, *C*).

DISCUSSION

Although CABG alone often results in improved LV function and MR, the latter does not resolve in a wide proportion of patients and predicts a poor prognosis.[14,15] Furthermore, mortalities in excess of 10% have been reported after ischemic MR repair at the time of CABG, and combined operations are less commonly performed in higher-risk patients if regurgitation is not severe.[3-7] Although previous reports support the benefits of repair also in mild-to-moderate ischemic MR, the optimal treatment of intermediate-degree ischemic MR remains a debated issue, and indications vary widely.[8-10]

Death

Operative mortality was 5%, similar to previous reports and lower than estimated with the EuroSCORE. All late deaths were caused by cardiac or vascular events, and heart failure was responsible for half of the cardiac-related mortality. The prevalence and modality of deaths reflect the severity of atherosclerotic disease and the unfavorable prognostic impact of underlying ventricular dysfunction, stressing the role of medical therapy for heart failure, resynchronization, and implantable defibrillators.

Baseline and early postoperative WMSI represented the only independent risk factors for late death. Unlike the roles of LVEF, LVESVI, and LV diameters,[6,12,16,17] the prognostic role of WMSI in patients with LV dysfunction has not been emphasized. Survival analysis outlined how patients with a preoperative WMSI of at least 2 showed a more evident late phase of increased risk of death, which was not correlated with MR recurrence. Ongoing trials may suggest adjunct procedures for patients with more severe dilatation and advanced cardiomyopathy.[18,19]

Adverse Events

Prolonged ICU stay, intra-aortic balloon pump, higher-dose catecholamine support was required in more than 75% of the cases. This finding reflects more advanced baseline LV remodeling, indicated by a higher LVESVI. Conversely, LVEF was a weaker predictor of high-dose inotropic support.

Overall, the probabilities of recurrent heart failure and 3+ MR at late follow-up were low and similar to results reported by others with an equal degree of annular downsizing.[12] WMSI was the only independent preoperative predictor of recurrent heart failure. Similarly, recurrent 2 + MR was

TABLE 4. Multivariable predictors of late outcome

	Adverse event					Left ventricular function and reverse remodeling*							
	Death			MR		LVEF			WMSI	LVESI			
	All cause	Cardiac related	Heart failure	≥3+	≥2+	Improved	Increase ≥5% from baseline	Increase ≥10% from baseline	Improved	Improved	Reduction ≥10%	Reduction ≥15% from baseline	Reduction ≥20% from baseline
LVEF, preoperative (%)													
P	—	—	—	—	—	.038	—	—	—	—	—	—	—
OR	—	—	—	—	—	0.95	—	—	—	—	—	—	—
95% CI	—	—	—	—	—	0.90–1.00	—	—	—	—	—	—	—
WMSI, preoperative†													
P	.011	.026	.012	—	—	—	—	.007	—	—	—	—	—
OR	1.23	1.23	1.35	—	—	—	—	1.51	—	—	—	—	—
95% CI	1.05–1.45	1.02–1.48	1.07–1.71	—	—	—	—	1.22–2.04	—	—	—	—	—
WMSI of 6 inferior segments, preoperative†													
P	—	—	—	—	.009	—	—	—	—	—	—	—	—
OR	—	—	—	—	1.17	—	—	—	—	—	—	—	—
95% CI	—	—	—	—	1.04–1.32	—	—	—	—	—	—	—	—
LVESVI, preoperative													
P	—	—	—	—	—	—	—	—	—	—	—	.009	.007
OR	—	—	—	—	—	—	—	—	—	—	—	1.03	1.04
95% CI	—	—	—	—	—	—	—	—	—	—	—	1.01–1.06	1.01–1.06
Sphericity ratio, preoperative†													
P	—	—	—	—	—	.032	—	—	—	—	—	—	—
OR	—	—	—	—	—	1.43	—	—	—	—	—	—	—
95% CI	—	—	—	—	—	1.03–1.99	—	—	—	—	—	—	—
Annuloplasty technique													
P	—	—	—	—	—	<.001	<.001	<.001	<.001	<.001	.001	<.001	<.001
OR	—	—	—	—	—	7.54	15.06	16.95	6.10	7.24	13.38	7.40	6.75
95% CI	—	—	—	—	—	3.30–17.24	5.40–41.98	4.20–68.33	2.58–14.44	2.72–19.25	2.93–61.06	2.82–19.41	2.44–18.72
Complicated course													
P	—	—	—	—	—	—	—	—	<.001	.021	—	—	—
OR	—	—	—	—	—	—	—	—	0.18	0.23	—	—	—
95% CI	—	—	—	—	—	—	—	—	0.08–0.45	0.07–0.80	—	—	—
LVEF, early postoperative (%)													
P	—	—	—	—	—	.007	—	—	—	.047	—	—	—
OR	—	—	—	—	—	0.92	—	—	—	0.92	—	—	—
95% CI	—	—	—	—	—	0.86–0.98	—	—	—	0.86–0.98	—	—	—
WMSI, early postoperative†													
P	.023	.045	—	—	—	.032	—	—	—	.013	—	—	—
OR	1.16	1.16	—	—	—	0.84	—	—	—	0.75	—	—	—
95% CI	1.02–1.36	1.00–1.34	—	—	—	0.72–0.99	—	—	—	0.63–0.94	—	—	—

TABLE 4. Continued

	Adverse event				Left ventricular function and reverse remodeling*							
	Death			MR	LVEF		WMSI	LVESI				
	All cause	Cardiac related	Heart failure	≥3+	≥2+	Improved	Increase ≥5% from baseline	Increase ≥10% from baseline	Improved	Improved	Reduction ≥10%	Reduction ≥15% from baseline	Reduction ≥20% from baseline
LVESVI, early postoperative													
P	—	—	.019	.017	.058	—	—	—	.002	.037	.047	—	—
OR	—	—	1.04	1.06	1.02	—	—	—	1.03	1.05	1.03	—	—
95% CI	—	—	1.01–1.08	1.01–1.12	1.00–1.05	—	—	—	1.01–1.05	1.00–1.09	1.00–1.06	—	—

MR, Mitral regurgitation; *LVEF*, left ventricular ejection fraction; *LVESVI*, left ventricular end-systolic volume index; *OR*, odds ratio; *CI*, confidence interval; *WMSI*, wall motion score index. *Variations of outcome variables from early postoperative measurements unless specified. †Hazard ratios refer to 0.1 increments of the predictive variable.

predicted by a worse baseline WMSInf. The predictive role of WMSInf may correlate with an increased posterior leaflet angle, which has been identified as an accurate predictor of adverse outcome after ischemic MR repair.[20] Furthermore, LVESVI early after surgery predicted all late adverse events at multivariable analysis, but baseline LVEF and LVESVI did not reach statistical significance. Only 1 patient underwent reoperation for recurrent MR, and no preoperative variable was able to predict recurrent 3+MR. Unlike previous reports, coaptation depth could not independently predict MR repair failure,[13] but a higher WMSInf was correlated with a higher incidence of late 2+MR, which may suggest a potential rationale for chord-sparing mitral valve replacement. In fact, this is now the source of a prospective randomized multicenter trial funded by the National Institutes of Health (ClinicalTrials.gov Identifier NCT00807040).

Early Postoperative LV Function

Patients with more compromised preoperative LVESVI, WMSI, or LVEF, or with an older infarction showed a higher probability of early reverse remodeling but a parallel incidence of residual higher LVESVI early after the operation, which reflects the severity of the underlying cardiomyopathy. A higher potential for early functional improvement may partially explain the lower than predicted operative mortality. These observations are in contrast with previous reports indicating that patients with more dilated ventricles are less likely to have responses.[12] In our series, however, baseline LVESVI was lower, possibly because MR was less severe and patients with 4+MR were excluded.

Interestingly, LVEF did not vary significantly early after repair, but our analysis suggests that LVEF improvement might be expected to occur more often in patients with higher LVESVI before surgery. LVEF of 36% or less emerged as a cutoff to discriminate patients more likely to show an early LVEF improvement. More importantly, all patients with baseline LVEF less than 30% had improvement. In this context, LVEF increase of at least 5% has been previously used to define functional recovery in patients with ventricular dysfunction undergoing CABG with or without associated MR repair.[6] We also tested for a LVEF increase of at least 10%, however, because a lower cutoff may underestimate the potential benefits of a combined operation, which predicts a comparatively greater LVESVI reduction than with isolated CABG despite similar baseline and early postoperative LVEF values.

Conversely, LVESVI is considered the preferred method to assess LV remodeling and function, especially in the presence of MR.[16] Baseline LVESVI was the strongest predictor of early postoperative LVEF and LVESVI and their respective variations, whereas a worse postoperative WMSI could be predicted in patients with left bundle branch block or previous anterior infarction. The possibility to predict an unfavorable residual LVESVI, at least 40 or 50 mL/m^2,

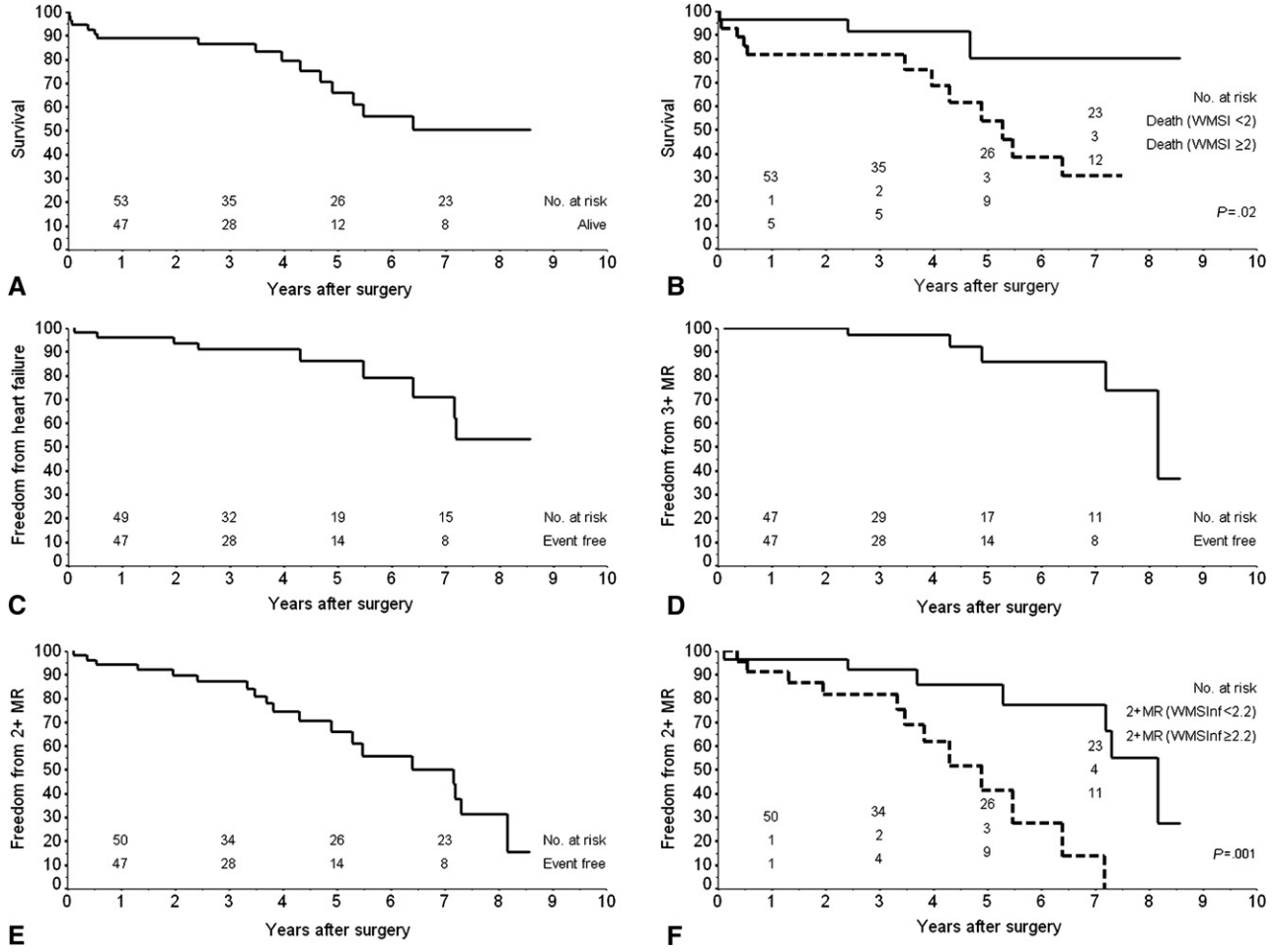

FIGURE 2. Kaplan–Meier plots illustrating survival (A and B) and freedom from adverse events (C–F). *WMSI,* wall motion score index; *WMSInf,* regional inferior wall motion score index; *MR,* mitral regurgitation.

represents an important issue, with the underlying rationale to indicate associated LV restoration procedures. In our experience, a baseline LVESVI of at least 54 mL/m^2 predicted an early postoperative LVESVI of at least 45 mL/m^2. This observation is similar to previous reports related to LV diameters and suggests that selected patients may be further evaluated with magnetic resonance imaging to define LV volumes more accurately before an associated ventricular surgical approach in the presence of a baseline LVESVI of at least 55 or 60 mL/m^2. In this context, the minority of patients with previous anterior myocardial infarction in our series was confined to earlier years, before 2002, reflecting the increasing incidence of ventricular reconstructive procedures in cardiac surgical practice. The role of associated ventricular restoration will further be clarified by randomized trials.[17] Conversely, no ventricular procedure is currently adopted in case of previous inferior infarction, and approaches under investigation, both clinically and experimentally, are aimed more at restoration of mitral leaflet coaptation than at ventricular volume reduction.[19,21]

Mitral Annular Stiffening and Late Reverse Remodeling

Baseline predictors of early and late functional recovery were similar, whereas the predictive trends of early postoperative variables were less clear-cut. Overall, late LVEF and LVESVI were more frequently improved in cases of more advanced ventricular disease in terms of LVEF, WMSI, and LVESVI. A more spherical ventricle, however, had less potential for late LVEF improvement. This outlines the importance not only of LV size and contractility but also of ventricular geometry, because undersized mitral annuloplasty restores a more physiologic sphericity.[22] Interestingly, sphericity has been recently reported to independently predict early functional recovery after valve replacement for aortic stenosis.[23] Conversely, the prognostic role of recurrent MR remains less defined with respect to the vicious cycle among MR itself, volume overload, and progressive remodeling.

Finally, the rigidity of annular restriction predicted late functional recovery. Undersized annuloplasty has been

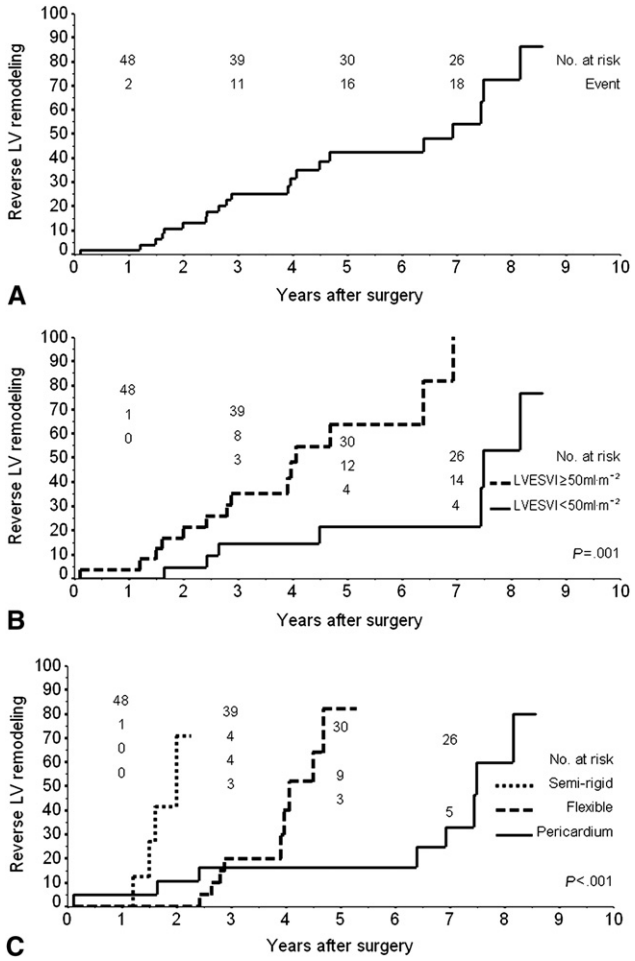

FIGURE 3. Kaplan–Meier plots illustrating occurrence of left ventricular *(LV)* reverse remodeling (A), expressed as late left ventricular end-systolic volume index *(LVESVI)* reduction of at least 20% from baseline, and effects of preoperative left ventricular end-systolic volume index (B) and different annuloplasty techniques (C).

experimentally correlated with reduced myocardial performance in the basal segments,[24] but this may be affected by the different tractions determined by suture techniques used in experimental models, especially in the anterobasal region. Basal contractility is substantially absent after inferoposterior infarction, however, which is the most common cause of ischemic MR. In our experience, a stiffer repair determined higher probabilities of improved late LVEF and WMSI and, most importantly, of reverse remodeling, as previously suggested.[11] Survival analysis also outlined an earlier timing of reverse remodeling. Previous observations outlined how the implantation of a complete rigid ring determines a more pronounced reduction of the anteroposterior mitral diameter and consequently a greater reduction of ventricular wall stress.[11] We did not implant a fully rigid ring, such as the Carpentier Classic, and a recent study did not report differences between Carpentier Classic and Physio rings.[17] MR recurrence with the Physio ring was lower than reported by others, however, in a recent analysis of 100 consecutive patients.[12] True comparisons between different devices are not possible because apparently equal sizes, as declared by manufacturers, correspond to different valve areas and diameters and yield different annular undersizing and potential for leaflet coaptation. For example, a size 24 Physio ring is similar to a size 26 Classic ring, and the latter has a comparatively shorter anteroposterior diameter. Thus ultimate ring size after repair (26.8 in our patients) may determine different results and is of little significance per se. We were unable to outline a predictive value of annular rigidity with respect to MR recurrence, but this has been well elucidated previously and is likely to be related to our small population, small number of adverse events, and small number of patients with a stiffer ring.[25] On theoretic grounds, the substantial absence of detrimental effects on myocardial function related to a more rigid annulus may allow us to expand indications for mitral valve replacement to selected patients with ischemic MR, provided that a chord-sparing technique is used.

Limitations

The major drawbacks are inherent in the retrospective nature of the study and the small number of patients. In addition, different annuloplasty techniques were not homogeneously distributed during the study period, with stiffer rings being progressively implanted in more recent years and in fewer patients. The pattern of techniques may have depended in part on different preferences of operating surgeons. Finally, the stiffening score used for analysis was arbitrarily defined and may not quantify stiffness from a mathematic standpoint. Statistical significance was reached with predictors entered as continuous nondichotomized variables, when appropriate, however, and the Cox analysis was repeated to test the appropriateness of the arbitrary stiffness coding, entering different numerical combinations of the score (namely, 1-2-3, 1-2-4, 1-3-4, 1-2-5, and 1-3-5) and obtaining the same *P* values with only minor differences in the corresponding hazard ratios.

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